Examining How Impedance Mismatches Impact Local Field Potential Recordings for Deep Brain Stimulation

A Thesis
Presented to
The Academic Faculty

By

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INTRODUCTION

During the early days of experimental psychology, a neurophysiologist by the name of Manfred Sakel set out to prove that he could treat schizophrenics by pharmacologically inducing a seizure (Wright, 1990). Sakel would eventually be proven right in 1935 by Ladislas Meduna. Their work eventually attracted the attention of Ugo Carletti, who had recently noticed that pigs could survive large voltages across their head. Carletti believed that instead of pharmacologically inducing a seizure, he could electrically induce one. In 1938, after many failed attempts to induce a seizure in a dog, Carletti and his team successfully induced a seizure in a person with schizophrenia. Electric convulsive therapy (ECT), as it would later become to be known, eventually gained immense popularity among psychiatrists. As technology and surgical procedures evolved, ECT became more refined.

Deep Brain Stimulation

Despite its popularity, ECT was believed to be crude. It eventually fell out of favor as a method of treating individuals with neurological disorders. However, an alternative form of electrical stimulation, Deep Brain Stimulation (DBS), would thrive.

DBS is a procedure in which electrode leads are surgically inserted into the brain. When connected to a pulse generator that is implanted in the patient's chest, the electrodes deliver a low voltage (< 3V) to the brain. DBS has been shown to be an effective procedure for numerous neurological disorders including; Parkinson's disease, obsessive compulsive disorder (OCD) and treatment resistant depression (TRD) (Deuschl et al, 2006, Greenburg et al,2006,Mayberg et al, 2008). Even though DBS has been around for many decades, the mechanisms behind it are not completely understood. This makes it difficult to predict how different stimulation sites and parameters affect a disorder's symptoms.

Pulse generators for Medotonic's DBS systems can be programed to output more than, 10 different pulse widths, 25 different frequencies, and 90 different voltages (Shykla et al.,2017). This means there are at a minimum 22,500 different stimulation settings that can be implemented *after* a surgeon has determined the ideal location for DBS lead placement.

Currently, the DBS stimulation settings are initialized during an hour-long session following the surgery. This labor-intensive process requires testing a variety of different settings and seeing how the patient responds to each of them. Given the wide number of different settings and the brains ability to adapt to environmental changes, the stimulation parameters cannot be set in one day. Over the course of multiple months, the patient will repeatedly have the stimulation parameters adjusted to fine tune the stimulation's effectiveness.

Despite the numerous visits, there is no guarantee that the optimal stimulation parameters will be set. Clinicians rely heavily on observable feedback (such as the intensity of tremors) and patient testimony to assess the effectiveness of a setting. These features may not provide the clinicians with significant enough information to optimize the stimulation parameters. Additionally, long term DBS has been linked with structural changes in this brain. This suggests that the effectiveness of different setting may change over time (Hartevelt, 2014).

Bi-Directional Deep Brain Stimulation

Ideally, DBS stimulation parameters would be adjusted constantly over time and would rely on the patient's brain state rather than visual cues. In the past 20 years, there has been a push to developing a closed-loop DBS system, which can do exactly that. Such a system would continuously record neural activity and adjust the stimulation accordingly. Currently, there is not a device that can precisely accomplish this. There are, however, numerous devices on the market which can record local neural activity to be used as a trigger for stimulation (such as Neuropace's RNS system) or to help clinicians adjust stimulation parameters (such as Medtronic's PC+S). These devices are sometimes referred to as bi-directional DBS or bdDBS. BdDBS systems can record local field potentials (LFPs) using the same electrode that stimulates the brain. This provides an effective method to analyze how DBS may impact local tissue.

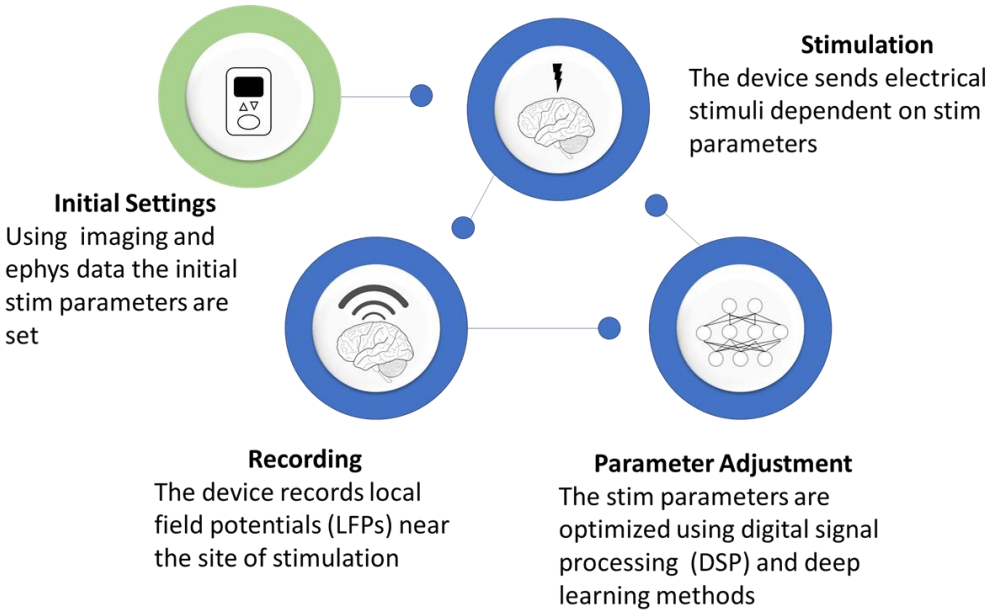

Figure 1. Flow diagram of closed loop deep brain stimulation

Local Field Potentials and the Emergence of Phase Amplitude Coupling

LFPs reflect the combined activity of neurons in the vicinity of the recording electrode. The area they encompass is highly debated, however, some studies have suggested that they may capture activity from regions as far out as a few millimeters (Kajikawa and Schroeder,2011). This can be a drawback to LFPs as it can make it difficult to interpret them. (Einevoll et al., 2011). They are, however, the preferred method for neural recordings because they can easily be incorporated into current DBS leads and are localized enough to examine how DBS effects the surrounding region.

In recent years, one of the interesting phenomenon captured from LFPs is phase amplitude coupling (PAC). PAC is a method of amplitude modulation for signals. In a PAC signal, the phase of a lower frequency component within the signal, modulates the amplitude of the higher frequencies. PAC is believed to be a form of dynamic communication between different brain regions (Canolty and Knight, 2010). Abnormal instances of PAC have also been confirmed in numerous neurological disorders including Parkinson's disease and TRD (de Hemptinne et al.,2013, Zheng and Zhang,2015). This has led to an interest in using PAC as critical feature in characterizing the impact of bdDBS for TRD.

Figure 2. PAC signal

Recording LFPs and Potential Drawbacks

Most bdDBS systems stimulate and record using an electrode that has a series of four concurrent leads. Bipolar stimulation is provided from two of the leads (usually two that are non-sequential) while LFP recordings are taken from the remaining two. This type of recording setup is called a differential recording setup (DR) because the output signal is the difference between the two recording contacts. An alternative recording setup, not widely used in bdDBS systems, is the referential recording (RR) setup. Here, recordings are made between an implanted contact and an external reference point. The DR setup is preferred over the RR setup because it can filter out noise from distal sources (Gabriel et al.,2018). In bdDBS, there is noise due to neural activity originating from outside the local electrode region. This noise can be picked up by the electrode due to a phenomenon called voltage conduction. The magnitude of the signal is, however, nearly equal on both recording channels. Therefore, taking the difference of the two recording channels can clean the recording.

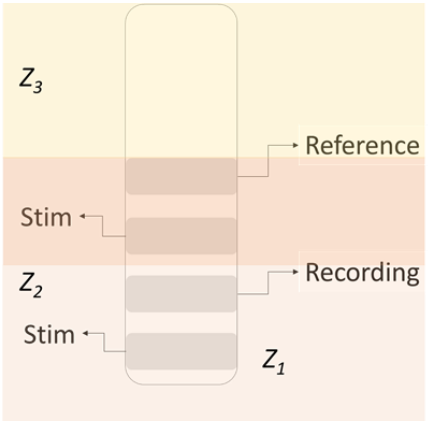

Figure 3. Differential recording setup
Z_1,Z_2,Z_3 Represent the impedance values of different tissues

The differential recording setup has been proven in both theory and in practice to be an effective method to clean LFP recordings. (Sasaki et al., 1983,Gabriel at al.2018). When modeling the differential recordings, researchers make calculations easier by assuming the brain is comprised of homogenous tissue. In reality, the brain is largely heterogenous and different regions have been shown to display different defining characteristics. Therefore, in some instances, the contacts used to record LFP signals may be in slightly different environments. More importantly, the tissue in these regions may have different impedance values. The resulting impedance mismatch can cause noise to be amplified rather than rejected by the differential recording setup. Prior to the advent of bdDBS, this theory has never been viewed as significant to the output of a differential recording setup. In the past, LFPs were usually recorded using versatile laboratory equipment. BdDBS systems on the other hand, have to deal with hardware constraints. Unlike laboratory equipment, bdDBS systems have lower rail voltages. This makes bdDBS systems vulnerable to gain compression if the LFP signal is amplified beyond the amplifiers capabilities. High levels of gain compression can easily be identified in an LFP as clipping. However, distortions to the LFP signal due to lower levels of gain compression may be near unnoticeable.

PURPOSE

This research seeks to understand how impedance mismatches between recording contacts in a bdDBS differential recording setup, impacts the fidelity of the output LFP recording and its features. There are three sections to this study:

1. confirming in a benchtop model that impedance mismatches can amplify signals to levels that can lead to gain compression in most bdDBS systems,
2. examining how the addition of gain compression impacts LFP features such as PAC and
3. identifying method to compensate for gain compression in LFP signals.

METHODS

Benchtop Testing

To verify that impedance mismatches can amplify a signal, this paper will examine how signals recorded from a mismatched system differ from those recorded from a nearly matched system. This verification will be done in a brain phantom rather than in a clinical setting with individual who have undergone bdDBS. This is primarily because clinical bdDBS studies are often difficult to conduct. The invasiveness of the procedure means researchers have to work with small cohorts and need to be cautious of any modifications that are made. While there has been some work into examining impedance mismatches from a clinical side, a benchtop modeling approach is easier to implement and can provide greater flexibility (Tiruvadi, 2018).

The brain phantom used in this study was an agarose based model adapted from work by Kandadai, Raymond and Shaw to develop a stable model that mimics the brain's low-frequency electrical properties. Such models have successfully been used in the past to perform analysis on EEG and transcranial electric stimulation (TES) devices (Hunold et al., 2018). However, these brain phantoms are homogenous and needed to be modified in order to replicate the impedance mismatches that normally occur in a differential recording setup. The modified brain phantom was developed by combining two brain phantoms, one with a high impedance (Z_{high}) and one with a low impedance (Z_{low}), into a single phantom. To develop the

Z_{low} phantom, a beaker was first filled with water and placed on a hot plate with a magnetic stirrer. As the water temperature rose, a mixture of agarose (1.2 percent by weight) and sodium chloride (1mg per ml of water) was added to the beaker. The solution was then allowed to heat up until the agarose and salt had completely dissolved. At this point, the solution was cooled to room temperature and then placed in a fridge until fully set into a gel (approximately 1 to 3 hours). The Z_{high} phantom was made in a similar fashion but with two differences; the amount of sodium chloride was reduced to 0.5mg per ml of water and the gel was not cooled to room temperature. Instead, it was cooled to around 50 °C, as to remain completely liquid. The unset gel was then added to the set Z_{low} gel and placed back in the fridge until completely set.

The impedance of each gel was determined using the impedance module in the data acquisition platform Real-Time eXperiment Interface (RTXi). A common multimeter could be used to the same effect. The impedance of the gels ranged from 1700 Ω to 3000 Ω and the mismatches ranged from 200 Ω to 500 Ω. The impedances are dependent on the molecular structure of the gel as it sets as well as the amount of sodium chloride added. While increasing the sodium concentration levels will decrease the impedance levels, the molecular structure of the gel is dependent on the concentration of agarose and how it sets. This confounding variable is believed to be the reason why each phantom did not have the same impedance values.

To replicate LFP signals, a signal generator was used to emit a 6 second, 100mV chirp that ranged from 0 to 100 Hz into the phantom. The faux LFP signals were recorded using a PC+S electrode that was inserted into the gel. Both the PC+S and signal generator electrodes were inserted in a 3D printed support array to keep them in place. To replicate the localized recording area of LFPs, the PC+S and stimulation electrodes were kept at a maximum distance of 3mm from each other. Differential recordings were made from two of the PC+S channels using a benchtop amplifier which had a gain of 100. Recordings were made with the PC+S at two different depths. At one depth, the PC+S electrode was inserted into only the first gel layer of the phantom. This was to replicate a near impedance matching scenario. At the second depth, the PC+S electrode was inserted at the interface between the two gel layers in the phantom. This setup was to model impedance mismatching by having one of the recording

contacts in the Z_{low} gel and the other contact in the Z_{high} gel. The output of both recording setups was recorded using RTXi.

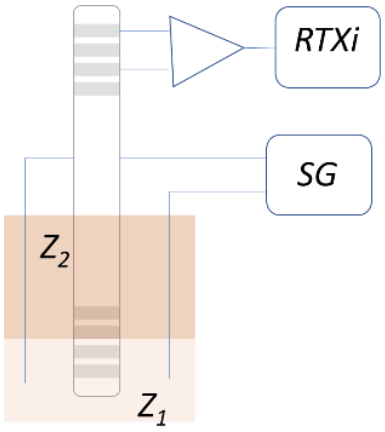

Figure 4. Benchtop setup

Gain Compression and PAC

Impedance mismatches are believed to drive recorded signals to levels beyond the hardware limitations of bdDBS systems. The resulting gain compression could distort the information in the LFP signal in any number of ways. This research is specifically examining the impact of gain compression on PAC because of its correlation with abnormal brain states and its use as a feature of interest in LFP analysis. Both a software and hardware approach were taken to model the effects of gain compression.

Preliminary modeling was done using the software approach. In brief, this approach was to pass a PAC signal through various amplifier models that exhibited different levels of gain compression. Coupling in the PAC signals where then examined using common PAC metrics. 1000 PAC signals were created as described per Tort et al. (2010). They each had a carrier frequency of 5 Hz and an envelope frequency of 50 Hz. The signals were then input into three different amplifier modeled in the Python script DBSpace at gains between 0 and 1. The three amplifiers include a perfect amplifier, which has a linear transfer function, a soft clipping amplifier, which has a tanh transfer function, and a hard clipping amplifier, which was linear from -1 to 1 but kept constant at either 1 or -1 everywhere else. The greatest level of gain compression would arise in the hard clipping amp, whereas the perfect amplifier would not

produce any gain distortion. The soft clipping amplifier created mild levels of gain compression. The amplified signals were then input in a Python library of metrics for PAC detection called CFCFilt (developed by Ali, 2016). Receiver Operating Characteristics curves (ROC) where then generated on each metrics performance as a method to evaluate the impact of gain compression on PAC.

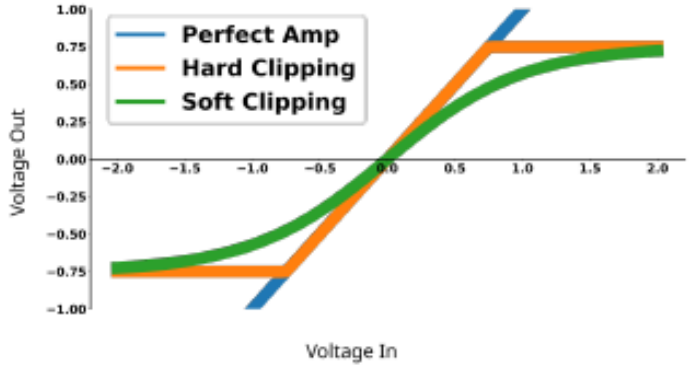

Figure 5. Transfer functions of different amplifier types
Adapted from Tiruvadi et al., 2019

In addition to the Python modeling, further testing was to be done by implementing the software approach onto an analog setup. However, due to time constraints this was not completed. A simple DC voltage amplifier was built to serve as a hard clipping amplifier. A soft clipping amplifier was then developed by adapting an overdrive effects pedal for electric guitars. Overdrive effect pedals produces their sound by soft clipping the input signal. Similar to the software approach, PAC signals with an envelope frequency of 5 Hz a carrier frequency of 50 Hz and an amplitude of 1V were to developed as described by Tort et al. Using the signal generator module in RTXi, the PAC signals were to be fed into the amplifiers with different levels of gain. The output signal was to then be recorded using RTXi and analyzed using CFCFilt.

Rectifying Information Loss Due to Gain Compression

BdDBS devices have a difficult line to tread. They must be able to record minute LFP signal while also outputting a stimulus that is many orders of magnitude larger. If any of the stimulus is leaked into the LFP recording, it could easily saturate the bdDBS system. In response, there

have been many digital and analog techniques developed to filter out the stimulus as to prevent this from happening (Rossi et al.,2009, Kent and Grill, 2012, Qian et al., 2017). However, these methods primarily rely on the notion that the stimulus frequency is well outside the frequency range of interest in LFP. Therefore, none of these methods would be appropriate for saturation that results from impedance mismatches. This thesis will briefly examine two methods to compensate for these signal distortions.

The first method is for improving the ability of PAC metrics in identify PAC in gain compressed LFP signals. A major issue with many of the current PAC metrics is that they rely on the linearity of PAC to classify signals. Gain compression can add non linearities to the output signal, thereby making it difficult to identify PAC. This is seen in the principle component analysis (PCA) method for PAC detection. Principle component analysis can identify PAC signals by mapping them onto a two-dimensional space and identifying a linear combination that can separate the carrier and envelope frequencies. An alternative approach is to implement kernel principle component analysis (kPCA). KPCA applies a kernel to the signal which maps it onto a higher dimensional space where it may be linear. Once linear, regular PCA can be applied to the signal. It may be helpful to note here that regular PCA is really a kPCA procedure that uses a linear kernel. To test the effectiveness of kPCA as a method to identifying PAC in gain compressed signals, a kernel approach was built on top of the PCA method currently implemented in CFCFilt. A variety of common kernels were implemented and then tested with gain compressed PAC signals.

Another method to reducing the impact of distortions on LFP signals is through the use of deep learning autoencoders. An autoencoder is a neural network that is specifically used to compress and decompress data. It is not a type of neural network, but rather an application of neural networks. The key goal of an autoencoder is to effectively automate the compression process for a specific set of data. An autoencoder consists of two components: an encoder and a decoder. The encoder compresses the data by projecting the data onto a smaller subspace. The decoder then projects the encoded information back onto the latent space. Autoencoders can be used for a variety of function, however, the most common use is for denoising

information. A denoising autoencoder encodes noisy information and then tries to project it onto the space of a clean signal.

Two different denoising autoencoder architectures were developed; a convolution neural network (CNN) and a long short-term memory (LSTM) recurrent neural network (RNN). The architectures of both autoencoders can be viewed below. Further work is necessary to train the neural network on LFP signals, however, the autoencoder's effectiveness was tested on denoising simple sinusoids. Both autoencoders were trained on a bank of 5000 sinusoids that ranged in frequency and had different levels of noise. The autoencoders were then optimized using hyperparameter optimization methods. Both autoencoders were built using the Python library Keras, which is an API for Google's machine learning platform Tensorflow. Training and optimization were done using the programing environment Google Collaboratory.

RESULTS

Benchtop Testing

Impedance mismatched setup was observed to amplify the differentially recorded signal. This phenomenon was not seen to the same degree in the near matched setup. The data obtained from the benchtop testing is currently being analyzed.

Gain Compression and PAC

ROC curves for different metrics ability to identify PAC indicated that they were significantly impaired by the addition of gain compression to the signal. The area under the curve (AUC) for nearly all metrics dropped from 0.95 in clean PAC signals to approximately 0.85 in distorted signals. Amplifying the PAC signals with a gain beyond 0.8 did not decrease the AUC significantly below 0.85. Furthermore, whether a soft clipping or hard clipping amplifier was used did not have a substantial impact on the AUC.

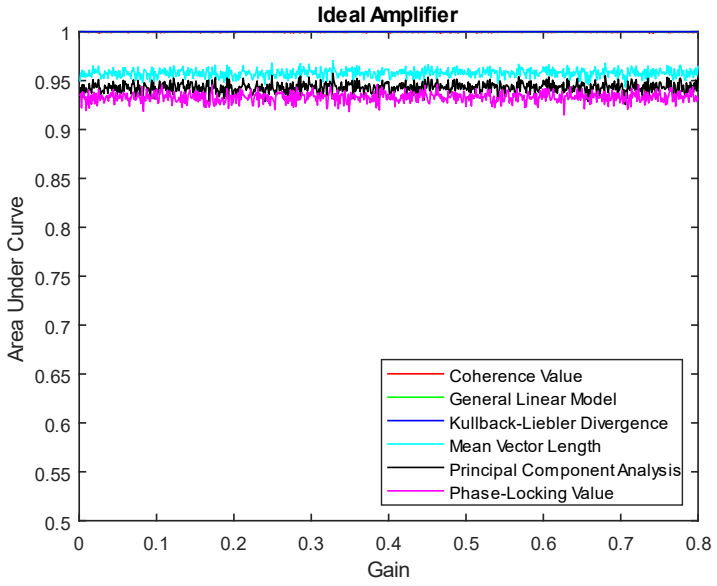

Figure 6. PAC Metrics for PAC Signals Amplified with an Ideal Amplifier

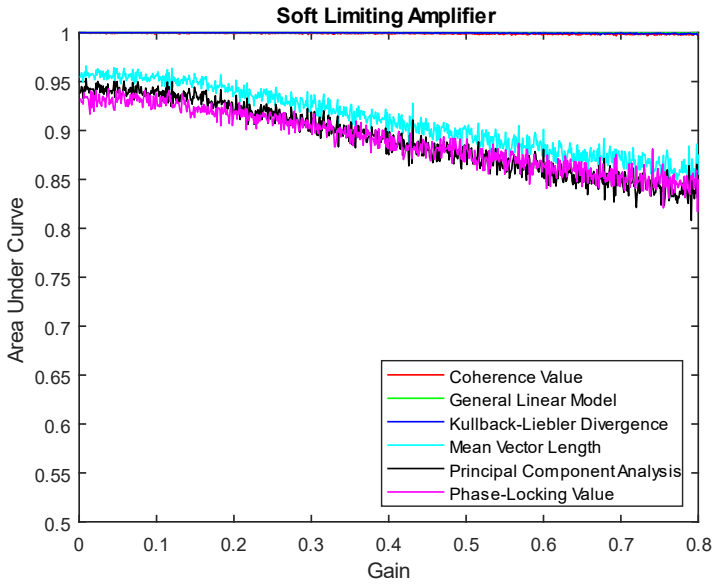

Figure 7. PAC Metrics for PAC Signals Amplified with a Soft Limiting Amplifier

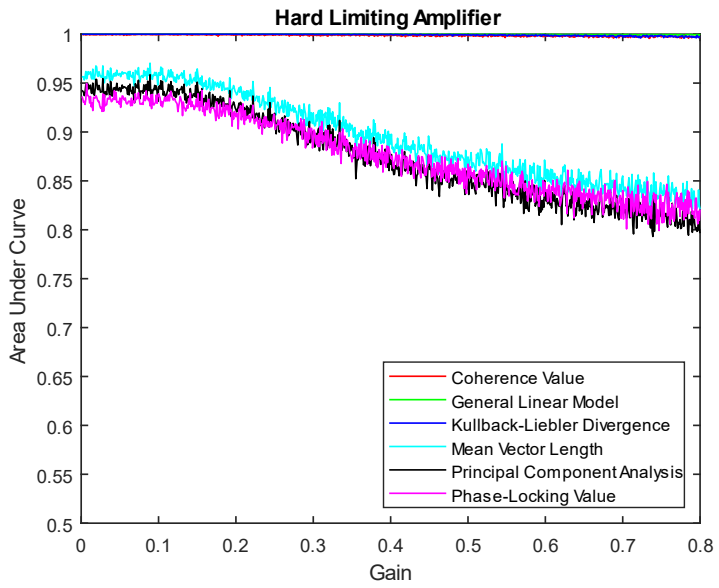

Figure 7. PAC Metrics for PAC Signals Amplified with an Soft and Hard Limiting Amplifier

kPCA

Currently the kPCA approach has only been implemented in Python. The CFCFilt package performs quite slowly in Python, therefore, it is currently impractical to create ROC curves of the kPCA approach. The effectiveness of different kernel functions on gain compressed PAC signals was examined qualitatively. The kernel functions examined include the linear, polynomial, sigmoid and arctanch kernels. However, to have these kernels perform well they need to be optimized. This has not currently been examined. Currently, the kPCA approach is still under development.

Autoencoder

Both autoencoders utilized time as the sole feature to denoise signals. The training and testing signals were input in 200 point sequences. While the CNN based autoencoder was able to clean the input signal the LSTM based autoencoder was unable to learn the characteristics of

the signal. The LSTM autoencoder required more time to train than the CNN model. However, both required more processing power than was available to be optimized.

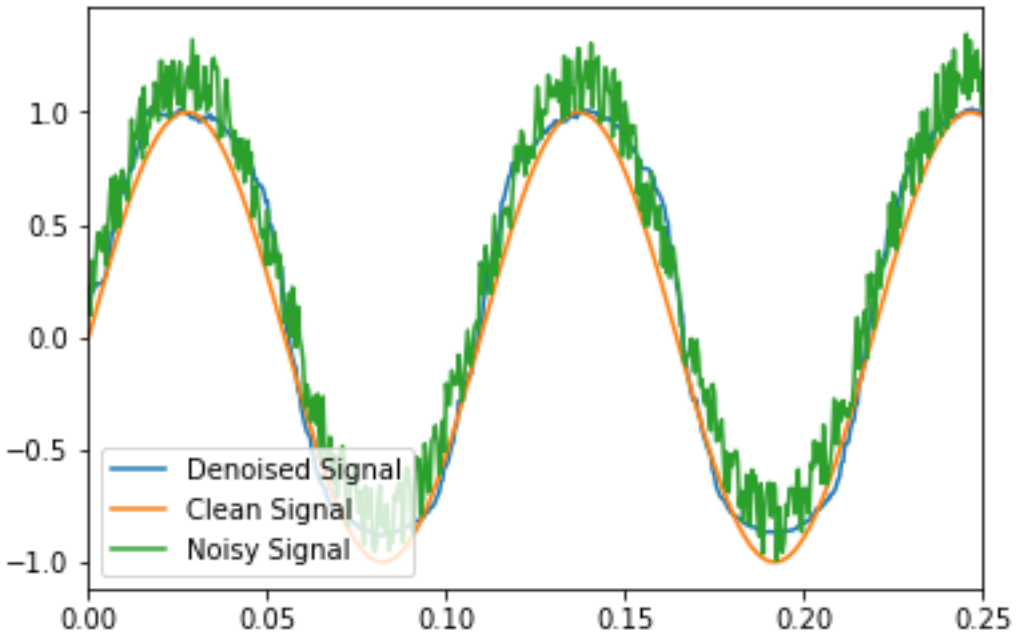

Figure 8. CNN autoencoder denoising a simple single frequency signal

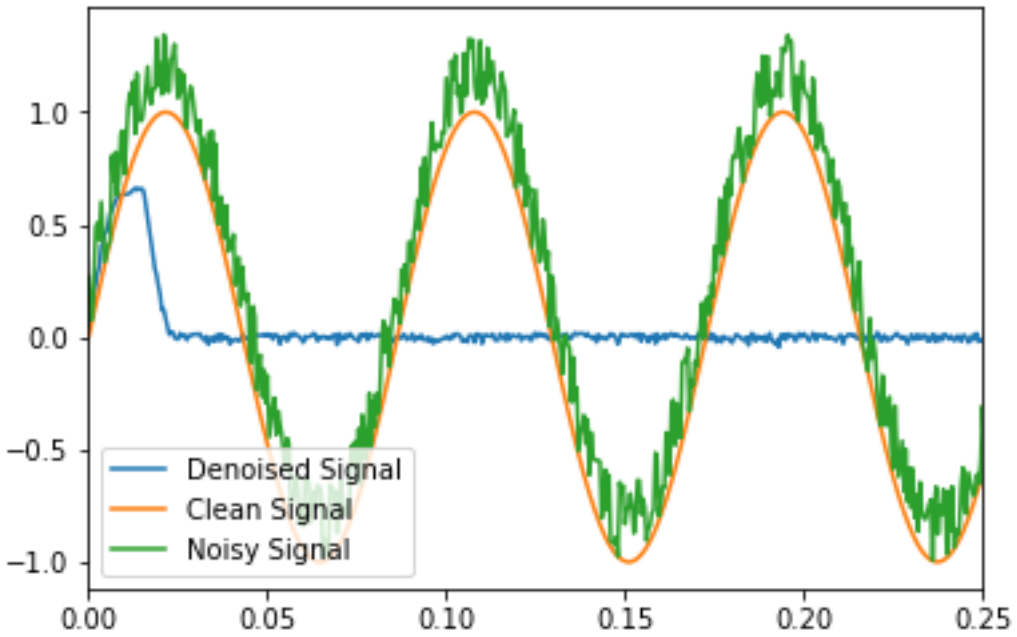

Figure 9. LSTM autoencoder attempting to denoise a signal

DISCUSSION

Benchtop modeling

A benchtop model was developed to mimic the response of an impedance mismatch on differentially recorded LFPs in bdDBS systems. While this novel model was functional, it faced many form factor and stabilities issues. There was tremendous difficulty in keeping the stimulation source and PC+S confined in a tight space. A combination of support beams and a printed 3D scaffold had to be used to prevent any of the electrodes from migrating in the phantom. While the phantom was also developed to mimic the elasticity of neural tissue, it was difficult to insert the PC+S lead into the gel. This was true even when a guidewire was inserted into the electrode. The work-around was to create a cavity with a toothpick for the electrode to fit into. The concern with this method is that it may create additional space than necessary to fit the electrode. Gaps near the electrode and gel interface could have resulted in large impedance values that would be difficult to identify. Furthermore, despite the phantom being developed for use at physiologically relevant temperatures, it would begin to liquify after an hour in room temperature. In general, this occurred only near the exposed top of the phantom. However, if this were to occur by the Z_{low} and Z_{high} interface there could be changes to the measured impedance mismatches.

Comparisons between the nearly matched recordings and the mismatched recordings indicate that impedance mismatches can amplify the recorded signal. This phenomenon is believed to be related to irregular instances of clipping that appear in LFP recordings made by bdDBS devices. If a large enough impedance mismatch occurs, the input signal the input signal can be amplified beyond the hardware limitations. The next stage in this work is to model the impedance mismatch model as a circuit. This could help provide an explanation as to why impedance mismatches amplify differentially recorded signals. It could also provide a relationship between the magnitude of the impedance mismatch and the resulting gain. Knowing this information will make it easier for future bdDBS devices to compensate for mismatch related gains.

Gain Compression and PAC

This study heavily relied on the python scripts CFCFilt and DBSpace to access the impact of gain compression on PAC. CFCFilt is a compilation of commonly used PAC metrics. These metrics include a general linear based metric, a Kullback-Leibler-based metric, a novel PCA method and more. Each of these metrics have different strengths and weaknesses (Rohit et al.,unpublished). DBSpace is a scrip to model LFP recordings made by a bdDBS device. It models three different amplifiers, each with a different type of clipping when saturated. When PAC signals were amplified through a saturated amplifier, the metrics in CFCFilter had difficulty in classifying signals. This is evident in the ROC graphs which shows that as the level of gain compression increased, the AUC decreased. ROC graphs are used to calculate the selectivity and sensitivity of a classifier. A decrease in the AUC does not specify whether the selectivity or the sensitivity of the classifier is decreasing. This makes it difficult to access why the metrics are performing poorly. One likely possibility is that gain compression adds non linearities to the PAC signal. The metrics in CFCFilt rely on the linearity of the signal to discriminate the carrier frequency from the envelope frequency. Therefore, adding non linearities to a PAC signal could prevent the metrics from classifying PAC signals. Another possible theory, although less likely, is that distortions in clean signal give rise to patterns that may be misconstrued as PAC signals.

With more studies suggesting that PAC is correlated with abnormal neurological behavior, there may be a push to use PAC as an indicator of different neurological disorders. PAC is commonly detected using the metrics available in CFCFilt. However, these metrics may not always be reliable. If gain compression does occur in the record signal, it could misclassify whether PAC exists in the signal. This could in turn lead doctors to misinterpret the patient's brain state. To avert this issue, a more versatile approach needs to be developed to identify PAC in an LFP signal.

kPCA and Autoencoders

Deep learning is a rapidly gowning field, but it is still primarily used for image analysis. Deep denoising autoencoder were developed as a method to remove noise from images. They are not commonly used to denoise time dependent signals. The common approach to implementing deep learning on time varying signals is to create a 2D CNN that is trained on a

spectrogram of the signal. The LSTM and CNN signals were not fully able to identify the training signals. A denoising autoencoder that follows the 2D CNN approach may be more successful. The denoising autoencoders developed for this project were designed to be easily implemented in a small recording device for real time filtering. While, the model may be able to make predictions in a reasonable time, it requires a significant amount of time and data to train and optimize. Such a concept still has potential. In the future, a denoising autoencoder may be able to invert distortions and filter out frequencies that were missed by analog and simpler digital filters.

CONCLUSION

This study has shown that impedance mismatches in a differential recording setup can lead to amplifier saturation, thereby distorting the information in the LFP signal. In other words, the fidelity of LFP recordings are constrained by a combination of the hardware's capabilities and the environment surrounding the recording electrode. This paper has also shown that signal processing methods could be implemented to mitigate the effects of impedance mismatches. If bdDBS continues to rely on LFP recordings, the continued development of mitigation methods could be beneficial for the advancement bdDBS systems. Ultimately, this will improve DBS and its effectiveness in treating individuals with neurological disorders.

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